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1. Your reference — JSnr/4-20921/P1 — 27 JUN 1996

2. Patent application number *(The Patent Office will fill in this part)* — **9613470.5**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CIBA-GEIGY AG,
Klybeckstrasse 141,
4002 Basle,
Switzerland.

Patents ADP number *(if you know it)* 259125600 1

If the applicant is a corporate body, give the country/state of its incorporation — Switzerland

4. Title of the invention — Small Solid Oral Dosage Form

5. Name of your agent *(if you have one)* — ABEL & IMRAY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Northumberland House,
303-306 High Holborn,
London.
WC1V 7LH

Patents ADP number *(if you know it)* — 174001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

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Description	8
Claim(s)	3
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
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11. I/We request the grant of a patent on the basis of this application.

Signature Abel & Imray Date

ABEL & IMRAY 27/06/96

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DUPLICATE

CIBA-GEIGY AG

CASE 4-20921/P1

SMALL SOLID ORAL DOSAGE FORM

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JSnr/VM

Small Solid Oral Dosage Form

The present invention relates to a solid oral dosage form containing valsartan combined with hydrochlorothiazide and to a process for the preparation of this solid oral dosage form.

A wide range of first-line therapy options is currently available for the treatment of hypertension. For instance, angiotension converting enzyme (ACE) inhibitors such as captopril are now used in therapy. Although the antihypertensive efficacy of ACE-inhibitors is well proven and the pharmacological profile appears to be firmly established, undesirable side effects may limit use in some patients.

A group of antihypertensive agents, angiotensin II receptor antagonists, reduce blood pressure by specific and selective blockade of the action of angiotensin at the receptor site, which is the last step in the renin-angiotensin-aldosterone cascade. As these therapeutic agents do not modulate the activity of converting enzymes and, therefore, do not potentiate bradykinin or Substance P, this class of therapeutic agents is not thought to be associated with side effects known to ACE inhibitors such as cough or angioneurotic edema.

Valsartan (Diovan®: Ciba-Geigy) is an especially preferred angiotensin II receptor antagonist which is effective at treating congestive heart failure and reducing blood pressure irrespective of age, sex, or race, and is also well tolerated. The preparation of valsartan is described in the U.S. Patent Specification No. 5 399 578 which is incorporated herein by reference.

Thiazide diuretics, e.g. hydrochlorothiazide, have been used for the treatment of hypertension.

WO 94/09778 describes pharmaceutical compositions containing angiotensin II receptor antagonists combined with diuretics. However, compositions containing valsartan combined with diuretics are not mentioned.

The oral administration of pharmaceutical agents formulated as tablets or capsules has certain advantages over parenteral administration such as i.v. or i.m.. A certain psychological aspect cannot be ignored. Diseases requiring treatment with "painful" injectable formulations are considered far more "serious" than those diseases being treated with oral dosage forms. The really important advantage of oral formulations is held to be their suitability for self-administration by the patient as opposed to parenteral formulations which have to be administered in most cases by a physician or paramedical personnel.

The possibility of self-administration by the patient is especially important for therapeutic agents that have to be administered chronically, which is usually the case in the treatment of hypertension.

In accordance with the invention a solid oral dosage form for the treatment of high blood pressure and congestive heart failure in mammals is provided. The solid oral dosage form contains valsartan combined with the diuretic agent hydrochlorothiazide. Also provided is a process for the preparation of this solid dosage form.

It has been found that valsartan, or a pharmaceutically acceptable salt thereof, combined in a dose range between about 10 and 250 mg with hydrochlorothiazide in a dose range range between about 6 and 60 mg, is suitable for more efficient treatment of hypertension. With these dose ranges of the combined active agents, valsartan is found to have a greater efficacy in reducing elevated blood pressure to normal levels than it would have if used at the same dose range in monotherapy. Moreover, when hydrochlorothiazide is being administered in combination with valsartan, the diuretic agent is more effective as compared to monotherapy at the dose range indicated. Particularly suitable is a dose range between about 50 and 100 mg valsartan and about 10 and 30 mg hydrochlorothiazide. Most preferred is a unit dose of about 80 mg valsartan and 12.5 mg hydrochlorothiazide and 160 mg valsartan and 12.5 mg hydrochlorothiazide. The weight ratio of valsartan or its pharmaceutically acceptable salt to hydrochlorothiazide is from about 1:6 to about 42:1, more preferably 2:1 to 10:1.

The presence of two different therapeutic agents requires the preparation of relatively large unit dosage forms to be administered orally. Capsules are undesirable since large capsule sizes must be selected for the voluminous fillings. In the event that tablets are preferred, the conventional method of wet granulation also results in the preparation of unit dosage forms of undesirably large sizes. This is particularly due to the fact that the wet granulation method requires the addition of considerable amounts of additives which are to be incorporated in the compressed dosage form with large amounts of active ingredients.

It has now been found that the combined active agents valsartan and hydrochlorothiazide are particularly suitable for the preparation of granulates by so called compression methods, particularly roller compaction methods. The granulates obtained by this method have a high content, especially more than 50 %, of active ingredients. The low amount of inert additives

present in the granulates is beneficial for the production of small sized tablets containing the combined active agents valsartan and hydrochlorothiazide.

The present invention relates to a solid oral dosage form which comprises as therapeutic agents

a) an effective amount of valsartan or a pharmaceutically acceptable salt thereof;
b) an effective amount of hydrochlorothiazide; and, as additives,
c) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods.

The present invention particularly relates to a solid oral dosage form, which comprises

a) a unit dose between about 10 and 250 mg, especially between about 50 and 100 mg, of valsartan or a pharmaceutically acceptable salt thereof; and
b) a unit dose between about 6 and 60 mg, especially between about 10 and 30 mg, of hydrochlorothiazide.

An especially preferred embodiment of the invention is a solid oral dosage form, which comprises

a) a unit dose of about 80 mg or 160 mg of valsartan or a pharmaceutically acceptable salt thereof; and
b) a unit dose of about 12.5 mg hydrochlorothiazide.

The present invention also relates to a process for the preparation of the solid oral dosage form, which process comprises:

grinding or sieving components a), b), and c); mixing the components; subjecting the mixture to compression; breaking the compressed masses to granulates; and compressing the granulates to a solid oral dosage form.

The terms used throughout this specification are defined as follows within the scope of the description of the present invention:

The term "compressed dosage form" embraces tablets or dragées that disintegrate in the stomach or in the interconnecting part of the gastrointestinal tract (duodenum) and which

are able to release the therapeutic agents valsartan and hydrochlorothiazide with or without controlled release.

Tablets or dragées (without control of drug release) are unit-dose solid dosage forms for oral administration that can be prepared by compression of granulates formed by compression, particularly compaction methods, with or without the addition of suitable excipients, by means of standard tabletting methods. Dragées are distinguished from tablets by providing them with an additional coating, typically a sugar, shellac, colored or film coating.

Compressed dosage forms with controlled release of therapeutic agent are distinguished by accelerated or delayed, as well as quantitatively controlled, release of drug. Thus tablets with accelerated release of therapeutic agent are formed with disintegrants such as cross-linked polyvinyl pyrrolidone (Polyplasdone®XL or Kollidon®CL) or reactive excipients (effervescent mixtures) that effect rapid disintegration of the tablet in the presence of water, for example so-called effervescent tablets that contain an acid in solid form, typically citric acid, which acts in water on a base containing chemically combined carbon dioxide, for example sodium hydrogencarbonate or sodium carbonate, and releases carbon dioxide.

Compressed dosage forms with delayed release and, preferably, quantitatively controlled release, of the therapeutic drug are defined in the technical literature by different terms such as enteric-coated tablets, tablets with modified drug release, release systems or oral therapeutic systems. These definitions meet a therapeutically determined objective, typically the delayed release of a drug to effect a reduction of local overconcentrations. This avoids the risk of irritation to gastric or intestinal mucosa. A wide range of dosage forms is known whose properties are defined by terms such as sustained release, controlled release, prolonged release, repeat or repeated release or delayed release. Some dosage forms are controlled release or sustained release forms that not only delay release of the active drug over a prolonged period of time but also release it in a controlled amount. Such dosage forms are known as oral osmotic systems (OROS), coated tablets, matrix tablets, film-coated tablets, press-coated tablets, multilayer tablets and the like.

A pharmaceutically acceptable salt of valsartan can be prepared in a manner known per se. Thus, for example, acid addition salts are obtained by treatment with an acid or a suitable ion exchange agent. Such salts can be converted to free compounds in a customary manner, by treatment with a suitable basic agent.

The preparation of valsartan is described in the U.S. Patent Specification No. 5 399 578 which is incorporated herein by reference.

Hydrochlorothiazide is a known therapeutic agent, which is useful for the treatment of hypertension.

Pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compaction methods are preferably excipients used for tabletting processes, especially those that are suitable for direct compression, e.g. powder binders such as starch, e.g. potato starch, wheat starch and corn starch, microcrystalline cellulose, e.g. products that are commercially available under the registered trademarks Avicel®, Filtrak®, Heweten® or Pharmacel®, highly dispersed silica, e.g. Aerosil®, mannitol, lactose, and also polyethylene glycol, preferably having a molecular mass of 4000 to 6000, crosslinked polyvinyl pyrrolidone (Crospovidone®, Polyplasdone®XL or Kollidon®XL), crosslinked carboxymethyl cellulose (Acdisol® CMC-XL), carboxymethyl cellulose [Nymcel® (Nyma)], carboxymethyl starch [Explotab® (Mendell) or Primojel® (Scholtens)], dicalcium phosphate, e.g. Emcompress®, or talcum. The addition of minor amounts of glidants, such as magnesium stearate, is also useful.

Particularly preferred as pharmaceutically acceptable additives are microcrystalline cellulose and crosslinked polyvinylpyrrolidone. Further excipients are siliconised talcum, aluminum stearate, stearic acid, palmitic acid, skimmed milk powder, stearyl, cetyl and myristyl alcohol, Lanette®0, paraffin or hydrogenated fats. With respect to tabletting, attention is drawn to the comprehensive technical literature on the subject.

The pharmaceutical compositions of the present invention are useful for lowering the blood pressure, either systolic or diastolic or both. The conditions for which the instant invention is useful include, without limitation, hypertension (whether of the malignant, essential, renovascular, diabetic, isolated systolic, or other secondary type), congestive heart failure, angina (whether stable or unstable), myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction (such as Alzheimer's), stroke, headache, and life extension. In addition, the compositions of the present invention are useful for treating chronic heart failure. The treatment of humans is particularly preferred.

In the process for the preparation of the solid oral dosage form, the individual components a), b) and c) are, if necessary, subjected to grinding or micronization methods. The components are milled either individually or together to particle sizes from about 0.1 μ to about 200 μ, preferably 1.0 μ to 100 μ. At least 90 % of the crystals of the components are present in these ranges. Particles of this size are obtained by conventional comminution methods, e.g. grinding in an air jet mill, hammer and screen mill, fine impact mill, ball mill or vibrator mill. Micronization is preferably effected by known methods using an ultrasonic disintegrator, e.g. of the BRANSON Sonifier type, or by stirring a suspension with a high speed agitator, for example with a stirrer of the HOMOREX type.

If necessary, the milled particles are sieved and mixed according to known methods. Compression involves the compaction of the dry components with special machinery, especially roller compactor, followed by milling and screening the comprimate prior to final compression into solid dosage forms such as tablets. Roller compactors utilize two rollers that revolve toward each other. By means of a hydraulic ram forcing one of the rollers against the other, the machine is capable of exerting strong compacting forces on the powdered materials that flow between the rollers. A compaction force of about 25 to 65 kN is particularly preferred. The powdered material is fed between the rollers by a screw conveyor system. A roller speed of about 1.3 to 7.5 rpm is particularly preferred. After passing through the rollers, the compacted mass resembles a thin ribbon in segments. The segments are then screened and/or milled by conventional grinding methods for the production of granules.

The present invention also relates to the comprimates and the granulates as obtained by the roller compaction method described above.

The compression of the granulates to tablet cores can be carried out in a conventional tabletting machine, e.g. in an EK-0 Korsch eccentric tabletting machine or a rotary compression machine, preferably at a compression greater than 2 kN. The tablet cores may vary in shape and be, for example, round, oval, oblong, cylindrical and the like, and may also vary in size depending on the concentration of the therapeutic agents.

They may furthermore be transparent, colourless, coloured and also marked so as to impart to these products an individual appearance and to make them instantly recognizable. The use of dyes can serve to enhance the appearance as well as to identify the compositions. Dyes suitable for use in pharmacy typically include carotinoids, iron oxides or chlorophyll.

The tablet cores can, if desired, be further processed in per se known manner to another solid dosage form, typically to dragées that are provided with an additional coating, e.g. a sugar, shellac, colored or film coating. Attention is drawn to the numerous known methods employed in the art of tabletting, e.g. spray coating in a fluidized bed, e.g. by the known methods using apparatus available from Aeromatic, Glatt, Wurster or Hüttlin, in a perforated pan by the Accela Cota method, or to the submerged sword coating method. The excipients commonly used in confectioning are employed in such methods.

In a preferred embodiment of the invention the tablets as obtained by the compression method of above preferably are slightly oval. Oval-shaped, in a narrower sense, are comprimates in which the two faces defining the height as being usually the smallest dimension are convexly curved about the longitudinal axis. Compacts of this form are especially suitable for the manufacture of film-coated dragées. The edges of the compacts are bevelled or rounded.

In a particularly preferred embodiment of the invention a solid oral dosage form is compressed in the form of a tablet having an oblong shape in which the range of the ratios of the dimensions length to width to height is approximately 2.5 to 5.0 (length) divided by 0.9 to 2.0 (width) divided by 1.0 (height) and in which the base and top faces of the tablet independently of one another are planar or convexly curved about the longitudinal axis; the side faces are planar, the end faces can be of any shape and the edges are optionally bevelled or rounded.

In a particularly preferred embodiment of the invention a solid oral dosage form is compressed from granulates in the form of a tablet of oblong shape in which the length is approximately 10.0 to 11.0 mm, the width approximately 5.0 to 6.0 mm and the height approximately 3.0 to 4.0 mm.

In a particularly preferred embodiment of the invention a solid oral dosage form is compressed from granulates in the form of a tablet of oblong shape in which the length is approximately 15.0 to 16.0 mm, the width approximately 6.0 to 7.0 mm and the height approximately 3.5 to 5.0 mm.

The following Examples illustrate the invention and the general operability thereof.

Example 1

Formula

valsartan	80.0 mg	(53.3 %)
hydrochlorothiazide	12.5 mg	(8.3 %)
colloidal anhydrous silica AEROSIL	1.5 mg	(1.0 %)
microcrystalline cellulose AVICEL	31.5 mg	(21.0 %)
polyvinylpyrrolidone CROSPOVIDONE	20.0 mg	(13.3 %)
magnesium stearate	4.5 mg	(3.0 %)
	150.0 mg	

Method

The components except a portion of the magnesium stearate are blended in a container mixer. The blended material is sieved and pre-blended for an additional period of time in a container mixer.The blended material is compacted using a roller compactor (Bepex Pharmapaktor L 200/50 P, Hosokawa Micron Group) by applying a compaction force of 25-65 kN and a roller speed of 1.3-7.5 rpm. The compacted material is sieved again and the remaining portion of the magnesium stearate is added and final blended in a container mixer. Then 150 mg of the homogenous mixture is compressed into tablets using ovaloid punches (10 x 5.2 mm). The tablets obtained have a length of 10.0-10.2 mm, a width of 5.2-5.4 mm and a height of 3.3-3.9 mm.

Example 2

Formula

valsartan	160.0 mg	(53.3 %)
hydrochlorothiazide	12.5 mg	(8.3 %)
colloidal anhydrous silica AEROSIL	3.0 mg	(1.0 %)
microcrystalline cellulose AVICEL	75.5 mg	(21.0 %)
polyvinylpyrrolidone CROSPOVIDONE	40.0 mg	(13.3 %)
magnesium stearate	9.0 mg	(3.0 %)
	300.0 mg	

A 300.0 mg tablet is formed according to the method described in Example 1. The tablets obtained have a length of 15.0-15.2 mm, a width of 6.0-6.2 mm and a height of 3.9-4.7 mm.

Claims

1. A solid oral dosage form which comprises as therapeutic agents
a) an effective amount of valsartan or a pharmaceutically acceptable salt thereof;
b) an effective amount of hydrochlorothiazide; and, as additives,
c) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods.

2. A solid oral dosage form according to claim 1 which comprises
a) a unit dose between about 10 and 250 mg of valsartan or a pharmaceutically acceptable salt thereof;
b) a unit dose between about 6 and 60 mg hydrochlorothiazide.

3. A solid oral dosage form according to claim 1 which comprises
a) a unit dose between about 50 and 100 mg of valsartan or a pharmaceutically acceptable salt thereof;
b) a unit dose between about 10 and 30 mg hydrochlorothiazide.

4. A solid oral dosage form according to claim 1 which comprises
a) a unit dose of about 80 mg or 160 mg of valsartan or a pharmaceutically acceptable salt thereof; and
b) a unit dose of about 12.5 mg hydrochlorothiazide.

5. A solid oral dosage form according to claim 1 which comprises
c) microcrystalline cellulose and crosslinked polyvinylpyrrolidone as pharmaceutically acceptable additives.

6. A solid oral dosage form according to claim 1 which comprises
a) a unit dose of about 80 mg or 160 mg of valsartan or a pharmaceutically acceptable salt thereof;
b) a unit dose of about 12.5 mg hydrochlorothiazide; and, as additives,
c) microcrystalline cellulose and crosslinked polyvinylpyrrolidone.

7. A solid oral dosage form according to claim 1 in the form of a tablet of an oblong shape in which the range of the ratios of the dimensions length to with to height is approximately 2.5 to 5.0 (length) divided by 0.9 to 2.0 (width) divided by 1.0 (height) and in which the base and top faces of the tablet independently of one another are planar or convexly curved about the longitudinal axis; the side faces are planar, the end faces can be of any shape and the edges are optionally bevelled or rounded;
which tablet comprises as therapeutic agents

a) an effective amount of valsartan or a pharmaceutically acceptable salt thereof;
b) an effective amount of hydrochlorothiazide; and as additives
c) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods.

8. A process for the preparation of a solid oral dosage form according to claim 1, which process comprises:
grinding or sieving components a), b), and c); mixing the components; subjecting the mixture to compression; breaking the compressed masses to granulates; and compressing the granulates to a solid oral dosage form.

9. A process according to claim 8, which process comprises subjecting the mixture of components a), b), and c) to compression by roller compaction methods.

10. A process according to claim 8 or 9, which process comprises compressing from granulates a tablet of an oblong shape in which the range of the ratios of the dimensions length to width to height is approximately 2.5 to 5.0 (length) divided by 0.9 to 2.0 (width) divided by 1.0 (height) and in which the base and top faces of the tablet independently of one another are planar or convexly curved about the longitudinal axis; the side faces are planar, the end faces can be of any shape and the edges are optionally bevelled or rounded.

11. A process according to any one of claims 7 to 10, which comprises compressing from granulates a tablet of oblong shape in which the length is approximately 10.0 to 11.0 mm, the width approximately 5.0 to 6.0 mm and the height approximately 3.0 to 4.0 mm.

12. A process according to any one of claims 7 to 10, which comprises compressing from granulates a tablet of oblong shape in which the length is approximately 15.0 to 16.0 mm, the width approximately 6.0 to 7.0 mm and the height approximately 3.5 to 5.0 mm.

13. The comprimates as obtained by the roller compaction method according to claim 9.

14. The granulates as obtained by the roller compaction method according to claim 9.

15. A solid oral dosage form according to claim 1 for use in a method for treatment of the human body by therapy.

Abstract of the Disclosure

The present invention relates to a solid oral dosage form in the form of tablets of small size which dosage form comprises as therapeutic agents

a) an effective amount of valsartan or a pharmaceutically acceptable salt thereof;

b) an effective amount of hydrochlorothiazide; and, as additives,

c) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods.